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TUMOUR REVIEW

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Ductal carcinoma *in situ* (DCIS) of the breast: evolving perspectives

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Ductal carcinoma *in situ* (DCIS) of the breast is an early, localized stage of carcinoma in the process of multistep breast carcinogenesis. The incidence of DCIS is increasing, mainly due to screening mammography, which results in diagnosing the disease in an increasing proportion of asymptomatic patients. Consequently, clinicians are being confronted with growing numbers of women who present with DCIS of the breast; thus, the concepts of managing such patients are assuming greater importance. The most common presentation is calcifications on mammography. DCIS is a biologically and morphologically heterogeneous disease. If left untreated, a significant proportion of these tumours will evolve into invasive cancer. However, when appropriately treated, the prognosis of DCIS is excellent. Optimal management of DCIS remains controversial. The goal in the treatment of patients with DCIS is to control local disease and prevent subsequent development of invasive cancer. For several decades, total mastectomy was the treatment of choice for DCIS and it should still be considered the standard of care, to which more conservative forms of treatment must be compared. Mastectomy is associated with a risk for chest wall recurrence of approximately 1%. Axillary lymph node dissection is not routinely recommended in the management of DCIS. However, mastectomy probably represents overtreatment in a substantial number of patients, especially those with small, mammographically detected lesions. Local excision alone has been suggested in carefully selected patients, whilst the rest of the patients undergoing breast-conservation surgery should be treated with breast irradiation. There is evidence that breast-conservation therapy is an effective option in the management of selected patients with DCIS. The use of radiotherapy after lumpectomy significantly decreases the rate of recurrence. Nuclear grade, presence of comedo necrosis, and margin involvement are the most commonly used predictors of the likelihood of recurrence. There is no role for adjuvant chemotherapy in the management of this disease. The role of tamoxifen in the treatment of DCIS is not clearly defined; tamoxifen should be given only in patients enrolled in clinical trials. Following breast-conservation therapy, about 50% of the tumours recur as invasive cancer. Most patients with recurrent disease can be treated effectively, usually by salvage mastectomy, but also in selected cases by breast-conservation therapy.

Key words: DCIS; conservative surgery; breast-conservation therapy; breast irradiation; tamoxifen; total mastectomy; mammography; lumpectomy; local excision; axillary lymph node dissection; recurrence.

"Experience with success or failure only enables the individual operator to justify methods"
Charles H. Mayo, M.D.

INTRODUCTION

'In-situ' carcinoma is the term used to describe proliferation of epithelial cells that have undergone malignant transformation but remain at their site of origin, confined by a basement membrane (1). Noninvasive (in-situ) breast cancer comprizes two separate entities: ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS). Because there

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are no lymphatics or blood vessels in the epithelial layer, DCIS and LCIS offer no risk for metastatic spread until malignant cells cross the basement membrane. Although LCIS is generally considered to be a marker of increased risk of future malignancy rather than an anatomic precursor of invasive disease, DCIS seems to be a more ominous lesion that is truly premalignant (2–4).

The increasing incidence of DCIS as a result of the widespread application of screening mammography, its biological heterogeneity and controversy about its treatment have made the management of this condition challenging. Clinicians are being confronted with an increasing number of patients presenting with DCIS of the breast, usually as in incidental finding on screening mammography. Therefore, the concepts of managing such patients are assuming greater importance. This emphasizes the need of understanding the biology of DCIS and ascertaining its appropriate management. The purpose of this paper is to present our current status of knowledge regarding the biological characters and management of DCIS.

HISTORICAL ASPECTS

Although breast carcinogenesis has been shown to be a multi-step phenomenon by histologic studies of breast tissue since the mid-19th century, the exact point at which actual malignancy begins in this progression has long been ignored (5). Many investigators have observed an intraepithelial phase, which Warren in 1907 described as "abnormal involution" (6). These in-situ carcinomas of the breast were identified and depicted in drawings, and later in photomicrographs, in the first quarter of the century. In 1908, a favourable ductal lesion was labelled "comedocarcinoma" (7) on the basis of gross and microscopic features of necrotic debris in the center of major lactiferous ducts that were filled with proliferating epithelium. "Comedocarcinoma" associated with fully developed carcinoma of the breast was subsequently distinguished from the "pure comedo tumor", the so-called "comedo-adenoma", a lesion believed to be benign but precancerous (7). Bloodgood noted that this particular type of breast cancer carried a favourable prognosis when treated by mastectomy (7). Cornil in Paris also described pre-invasive lesions in 1908 (9), Ewing in 1919 (10), and later by Foote and Stewart in 1941 (11). In 1932, Broders defined carcinoma *in situ* as "a condition in which malignant epithelial cells and their progeny are found in or near positions occupied by their ancestors before the ancestors underwent malignant transformation" (12); he also emphasized the unique biological implications of the in-situ carcinoma related to its potentially curability by local excision alone. The lesion was first named "ductal carcinoma *in situ*" (DCIS) in 1960, at which time it was considered a malignancy that was associated with a favourable prognosis but was potentially dangerous and required mastectomy (13). The term "minimal breast cancer", which encompassed LCIS, DCIS, and minimally invasive lesions of less than 5 mm in size, was introduced in the 1970s (14, 15); this term has been abandoned today, because the biologic behaviors, prognosis, and treatment strategies for each entity are entirely different.

Initially, it was believed that DCIS originated in extralobular major ducts, whereas LCIS originated in lobules. In 1941, Muir illustrated DCIS originating in the terminal duct/lobular unit (TDLU) and designated it as "intra-acinous carcinoma" (16). Wellings, Jensen, and Marcum (17) clearly demonstrated that both duct and lobular carcinoma *in situ*, as well as a host of other specific breast lesions, originate predominantly in the TDLU. It is now well known that the morphological differences between LCIS and DCIS reflect a different histogenesis but also a different biologic behavior. LCIS is generally considered to be a marker of increased risk of future invasive malignancy rather than an actual, anatomic precursor of such and most surgeons currently have adopted a nonoperative surveillance of women with this diagnosis (2, 3). Prophylactic mastectomy may be another option for selected women with LCIS, especially in the presence of other associated risk factors (e.g., strong family history). DCIS, however, appears to behave as a truly premalignant lesion (3, 4).

EPIDEMIOLOGY

The exact incidence of DCIS in the general population is unknown and has been a source of controversy. Before the 1980s, when most cases of breast carcinoma were detected by physical examination, DCIS comprized less than 1% of all breast biopsies and less than 5% of all breast malignancies. At that time, DCIS comprized only about one-fourth of all non-invasive breast malignancies (18,19). Since the introduction of routine screening mammography in the 1980s, the incidence of DCIS has increased dramatically (20, 21). The increased recognition of this entity among pathologists contributed also to this increase of incidence (21, 22). Age-adjusted DCIS incidence rates increased an average of 3.9% annually from 1973 to 1983 and 17.5% annually from 1983 to 1992 (22). Interestingly, the rate of increase in

incidence has been higher for DCIS than for any other type of breast cancer (23). The reported incidence in women 50 years of age or older increased 235% from 1979 to 1986; in contrast, the incidence of invasive cancer increased 50% (24). Further increases have occurred since then.

DCIS now represents 10–15% of all new breast cancers diagnosed in the United States (22, 25, 26) and accounts for 30–50% of cancers detected by screening mammography in women less than age 50 years and 15–25% in women over age 50; it also comprizes approximately 7–10% of all breast biopsies (22, 27, 28). Furthermore, the average size or extent of DCIS in the breast is dramatically reduced, from an average approximate 60 mm in those few cases detected by palpation to 10 mm or less in those detected mammographically (29).

Interestingly, a greater increase in the frequency of diagnosis of DCIS compared to LCIS has been observed. While the ratio of LCIS to DCIS in series of breast biopsies before the advent of mammography was 2:1 to 3:1 (18), this proportion was reversed in favour of DCIS with an average ratio of 3:1 and ranges as great as 6.4:1 in more recent series (30, 31). Probably this is due to the characteristic mammographic manifestations of DCIS (microcalcifications), which LCIS does not have (32).

The median age reported for patients with DCIS is 45–65 years, which is not different from that reported for patients with invasive carcinoma. Some studies have noted a trend toward a lower median age in patients with DCIS detected in screening mammography. The frequency of a family history of breast cancer among first degree relatives of patients with DCIS (10–35%) is not different from that reported for women with invasive breast malignancy (33). DCIS also occurs in men and represents about 5% of all cases of male breast cancer (34).

The results of autopsy studies suggest that latent DCIS is relatively common, ranging from 0.2 to 18% in random autopsy series or series confined to women who died of causes other than breast cancer or who were not known to have had breast cancer at the time of death (35–39). These autopsy studies are important in helping us understand the natural history of DCIS. From these studies, it was estimated that no more than one third of all intraductal carcinomas will progress to invasive breast cancer (36). The clinical implication of this remains unclear, however. If a large proportion of cases of DCIS never become clinically apparent or life-threatening, it may be that a large proportion of women with mammographically detected DCIS will not benefit from treatment. This underlines the significance of understanding the natural history of DCIS, which have obvious clinical implications.

NATURAL HISTORY

The information available on the risk of progression from DCIS to invasive breast cancer is extremely limited. This is mainly due to the fact that in the past, most patients with DCIS were treated by mastectomy, which eliminated the possibility of studying the natural history of this lesion. The only studies to address this issue have been those in which patients with DCIS were initially misdiagnosed with benign lesions who were found to be DCIS on subsequent analysis and received no further treatment after excisional biopsy (18, 40–44). The number of the patients in those studies was relatively small (range, 8–25) and most of these cases were low-grade non-comedo DCIS with uncertain margins. During the follow-up period, ipsilateral invasive breast cancer developed in a large percentage of those women (range, 15–75%), usually within 10 years of biopsy. In nearly all patients in those studies, the recurrent invasive cancer occurred at or near the site of the original biopsy, indicating incomplete excision rather than multifocality of the tumour. These studies showed that DCIS treated with simple excision alone is associated with a significant risk for the development of subsequent invasive cancer, up to 11-fold higher than the risk expected in the general population. These data support the concept of DCIS as an anatomical 'forerunner' to invasive breast cancer.

There is, however, evidence that not all DCIS progress to invasive breast cancer. This is supported by the increased incidence of latent DCIS found on autopsy studies (see above, Epidemiology); these studies showed a higher incidence of detection of DCIS than is evident in the general population, suggesting that not all DCIS become clinically significant (35–39). Insight into the biological importance of DCIS can also be obtained from studies indicating that foci of the disease are frequently detected in the contralateral breast of women with invasive breast cancer (45). These studies found a discrepancy between this incidence and the risk of a subsequent clinically evident cancer in the opposite breast. For example, Alpers and Wellings found DCIS in 48% of breasts contralateral to cancer-containing breasts (37), yet the cumulative risk of opposite-breast cancer 20 years after diagnosis of the initial tumour has been reported to be only 12.5% (45). These data suggest that not all cases of histologically detectable DCIS will progress to clinically 'important' cancers (45, 46). We can not distinguish, however, which DCIS will progress to an invasive breast cancer and which will remain latent (and for how long).

PATHOLOGY

DCIS is a heterogeneous entity with several morphologic variants that markedly differ in gross and histologic appearance, cellular characteristics, and clinical behaviour. As previously reported, DCIS arise from ductal epithelium in the region of the terminal ductal lobular unit (TDLU) (16, 17, 47) and probably represents one stage in a continuum between atypical ductal hyperplasia and invasive carcinoma in the multistep breast carcinogenesis (Figure 1 A and B).

The earliest phases of DCIS are characterized microscopically by a proliferation of the inner cuboidal layer of epithelial cells in the lactiferous ducts of TDLU to form micropapillary or papillary ingrowths into the lumen. At this stage, the cells of this pattern are generally well differentiated without evidence of significant pleomorphism, atypia or mitoses, which may lead to difficulty in differentiating DCIS from benign hyperplasia (48). As this pattern of DCIS progresses, these ingrowths from a bridging network within the ductal lumen until punched-out, rounded spaces remain interspersed among epithelial arcades ('Roman bridges' or 'cartwheels'), which themselves show some degree of atypia and loss of polarity. This is the 'cribriform' growth pattern of DCIS (16, 49, 50). When cellular proliferation obliterates all spaces, the 'solid' histologic form of DCIS results, which is characterized by ductal distention with more anaplastic cells and mitotic figures. As growth continues, the cells in the center of ducts outstrip their blood supply and become necrotic, leading to the classic picture of the 'comedo' pattern (51). There may also be an associated inflammatory reaction, stromal response, or lymphoid infiltration surrounding the duct that may render the lesion clinically palpable. Calcium deposition usually occurs in areas of rapid growth and necrosis, leading to the most typical mammographic appearance of DCIS (microcalcifications) (52). Cribriform, comedo, and micropapillary are the most common subtypes, although two or more patterns coexist in up to 50% of cases (32). Through all these phases, the overall ductal picture remains intact, with no invasion of the malignant cells into the surrounding stroma (53). Although ultrastructural studies have shown variable levels of disruption of the basal lamina in cases of DCIS, most pathologists currently accept diagnosis by light microscopy only (54).

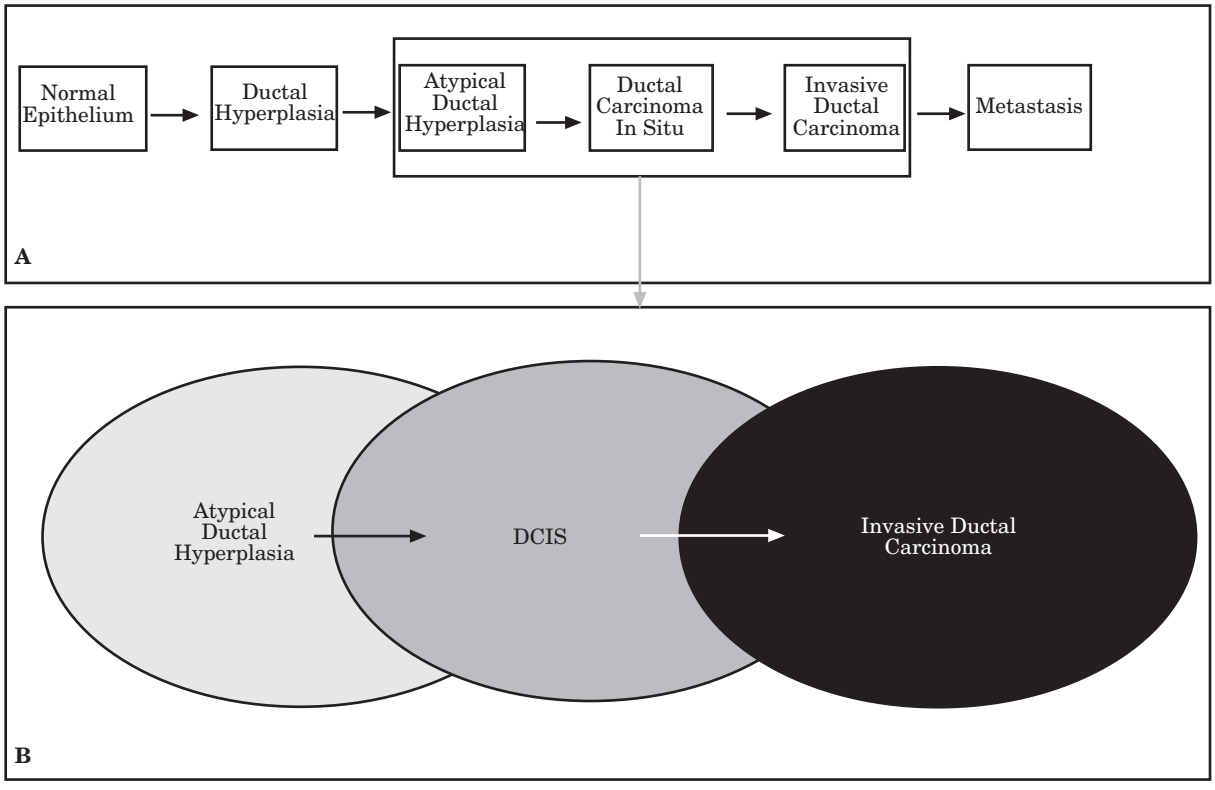

Figure 1 Multistep breast carcinogenesis (A). DCIS represents one intermediate stage in the spectrum between atypical ductal hyperplasia and invasive cancer. Sometimes, the differential diagnosis between DCIS and atypical ductal hyperplasia may be difficult (B); moreover, these two entities may coexist. At the other end of the spectrum, the identification of invasive cancer may be problematic, either because of a sampling error or because DCIS may be associated with periductal fibrosis, inflammation, and distortion of the involved ducts, making histological evaluation problematic for the detection of invasion and identification of invasive cancer (B).

In most cases, the histologic diagnosis of DCIS is relatively straightforward; however, several aspects of the differential diagnosis are noteworthy. At one end of the spectrum, it may occasionally be difficult to distinguish benign ductal hyperplasia – particularly when associated with atypia – from DCIS (Fig. 1 B). This distinction may be subjective and arbitrary, even among experienced pathologists (53). Benign ductal atypical hyperplasia may coexist with DCIS and therefore any specimen showing suspicious or atypical changes should undergo further sectioning to exclude the presence of DCIS, which may otherwise be undetected. Its detection is, therefore, dependent to some degree on the diligence of the pathologist. At the other end of the spectrum, the identification of small foci of stromal invasion may be extremely difficult, either because of sampling error or because the DCIS may be associated with fibrosis and inflammation in the surrounding stroma, with distortion of the involved ducts. The pathologist should therefore examine several additional sections of any specimen containing DCIS to exclude invasion, because of the significant change in management this may entail (45). Despite these difficulties, if careful attention is paid to standardized diagnostic criteria, this distinction can be made with reasonable certainty (55–57). Sometimes, LCIS and DCIS may co-exist and this may lead to some diagnostic confusion (50, 58). This may be further exacerbated by the occasional spread of LCIS into the mammary ducts. On the contrary, when DCIS is extensive, it is frequently seen within obviously lobular structures, the so-called "cancerization of lobules" (53).

The aforementioned difficulties indicate that a careful review of permanent sections is required for a consistently accurate diagnosis. Distinguishing between atypical ductal hyperplasia and DCIS may be impossible in frozen-section preparations (59). Furthermore, small foci of microinvasion may be lost or rendered uninterpretable by freezing artifacts. The limited amount of diseased tissue available for histological analysis and tumour marker assays is an important consideration for small, mammographically detected DCIS. These limitations and problems of frozen-section should be kept in mind during the surgical decision-making process. Close cooperation with an experienced pathologist is essential.

Information regarding hormone receptor activity, DNA morphology and proliferative activity, ultrastructural analysis, and oncogene expression enhances the understanding of tumour biology and may assist clinicians in difficult management decisions and in the distinction between DCIS and benign variants (60). State-of-the-art immunohistochemical techniques enable us to perform many of these assays on the same tissue used for histology or cytology (31). This may be especially important for DCIS due to the usually limited amount of tissue available for histologic examination and tumour marker assays (49).

The histological variants of DCIS correlate with the biological behaviour of the tumour and its prognosis. Solid and cribriform DCIS are rarely multicentric or microinvasive; micropapillary DCIS are often multicentric, rarely microinvasive (58, 61). The comedo type correlates with greater size of the tumour, higher nuclear grade, increased incidence of multicentricity and micro-invasion, increased recurrence rates, and shorter disease-free interval to recurrence (4, 45, 46, 62–65). Additional indicators of an aggressive biological behavior and poor prognosis associated with comedo DCIS are high DNA proliferative activity, aneuploid DNA patterns, chromosomal abnormalities, *c-erb*B-2 oncogene amplification, lack of estrogen/progesterone receptor expression, p53 overexpression, heat shock protein and metallothionin expression, etc. (33, 66–71). In view of these findings, some investigators classified DCIS only as comedo or noncomedo subtypes (72, 73).

Multicentricity

Multicentricity is defined as DCIS in a quadrant other than the index quadrant. Obviously, multicentricity is of crucial importance in determining the feasibility of breast-conservation therapy as a treatment option because resection of the affected area must encompass the entire tumor. The reported incidence of multicentricity varies from 18 to 60%. This wide range is probably due – at least in part – to differences in histopathologic techniques and definitions, and is more likely around 30–40% (33, 74–76). Nowadays, the biologic significance of multicentricity has been questioned, because 96% of all local recurrences after treatment for DCIS occur in the same quadrant as the index lesion, implicating residual untreated disease rather than multicentricity (77) (see below, NSABP–B06 trial). Mammary lobules are not constrained by the artificially imposed quadrant segregation and therefore contiguous intraductal spread may be interpreted as multicentricity on cursory pathologic examination (see below, Multifocality). Current data do not support the concept of multicentric disease (74).

Multifocality

Multifocality is generally considered to be present when separate foci of DCIS occur more than 5 mm

apart in the same breast quadrant. The results of the NSABP-B06 trial, in which the use of modified radical mastectomy was compared with that of segmentectomy plus radiotherapy for invasive breast cancer, support the hypothesis that multifocality (same quadrant) may be clinically more important than multicentricity (other quadrant). This study inadvertedly included 78 patients whose DCIS had been incorrectly diagnosed as invasive disease. All local recurrences after breast-conservation therapy and all residual carcinomatous foci in the mastectomy specimen were in the quadrant of the initial lesion, minimizing multicentricity, as a contraindication for the conservative surgical treatment of DCIS (77). However, it is possible that 'multifocal' disease may in fact represent intraductal spread from a single focus of DCIS. Indeed, Holland *et al.* demonstrated that multifocal lesions that appeared separate by traditional pathologic techniques were actually originating from the same focus in 81 of 82 mastectomy specimens (78).

Bilaterality

Bilaterality is another feature of DCIS (Table 1) (31, 44, 50, 79–83). The incidence of bilaterality is lower in DCIS than in LCIS. Bilaterality occurs in about 10–15% of patients with DCIS (31). There is evidence that the bilaterality does not affect survival (84). This is supported by the fact that the rate of development of contralateral clinically evident breast carcinoma is much lower than the reported incidence of bilaterality and by the findings of autopsy studies reporting higher rates of occult DCIS than clinically evident cancers (see above, natural history).

Microinvasion

DCIS with microinvasion is generally defined as a predominantly noninvasive lesion with foci of invasive cancer, each measuring less than 1 mm. Larger areas of invasive growth are termed "minimally invasive carcinoma" (T1a=1–5 mm and T1b=5–10 mm) (29, 85). The incidence of microinvasion varies according to the size and extent of the DCIS. For example, Lagios *et al.*, (75) reported a 2% incidence of microinvasion in patients with DCIS measuring less than 25 mm, compared with a 29% incidence of microinvasion in index lesions larger than 26 mm. Recently, investigators have questioned the significance of distinguishing pure DCIS from DCIS with microinvasion (86). However, it appears that the presence of microinvasion signifies a theoretically different disease entity, with the potential – albeit minimal – for metastatic disease. This has obvious clinical implications, since patients with pure DCIS are not candidates for axillary lymph node dissection nor for adjuvant systemic therapy following mastectomy or breast-conservation therapy. As previously noted, the diagnosis of microinvasion may be a challenge for the pathologist. In addition to the aforementioned difficulties, there is a number of factors that can further complicate the histologic examination and lead to misdiagnosis or misinterpretation of microinvasion. For example, microinvasion can be mimicked by artifacts, duct sclerosis, entrapment, etc. From a technical point of view, the error rate can be reduced using some simple measures, such as avoidance of higher electrocautery voltages or crushing of the tissue (especially at the edge of the specimen) when excising diagnostic biopsy material, adequate fixation time, etc. (29).

Molecular biology

The heterogeneity of DCIS is also apparent at the molecular level, in which specimens of DCIS show several genetic alterations (74). Overexpression of *c-erb*B-2 occurs in 0–50% of low-grade DCIS, compared with 50–100% of high grade DCIS (87). *c-erb*B-2 overexpression is more common in the comedo subtype

Table 1 Development of contralateral invasive and non-invasive breast cancer after DCIS

Number of patients	Follow-up years	Women-years	DCIS	Invasive breast cancer	Total (DCIS + Invasive)	Ref #
101	5	505	2	0	2	79
70	8	560	1	2	3	80
116	9	1044	0	0	0	81
183	10	1830	1	5	6	82
80	17.5	1400	0	1	1	44
1929	4.5	8681	21	53	74	83
Total		14020	25(*)	61 (*)	86	

* This represents an annual contralateral cancer rate of 0.02% for women with DCIS, compared with 0.6% for patients with invasive cancer.

DCIS. Of note, *c-erb*B-2 overexpression is seen in only 20–25% of cases of invasive breast cancer (88). Mutations of the *p53* gene are present in DCIS and are more common in the comedo and high-grade DCIS; the expression of *p53* ranged from 0–21% among low-grade DCIS to 3–67% among high grade DCIS (89, 90). Allelic imbalance (loss of intensity of one allele) for the *BRCA1* gene has been found in 74% of cases of the tumour (91). Overexpression of cyclinD1 is present in nearly 90% of malignant breast lesions (both DCIS and invasive breast cancer) (92).

DIAGNOSIS

Clinical presentation

In the past, patients with DCIS presented with a palpable mass, nipple discharge, or Paget's disease of the nipple. Occasionally, DCIS was an incidental finding in an otherwise benign biopsy specimen. Frequently, the palpable lesion was large, and in up to 25% of cases demonstrated associated foci of invasive disease. The presence of occult invasion in these large lesions as well as a 10% incidence of axillary lymph node metastasis led to the same treatment recommendations for patients with DCIS as for those with invasive breast cancer. Now, that screening mammography is more widely available, palpable or symptomatic DCIS with occult invasion and lymph node metastasis is rarely encountered, leading to a reassessment of treatment strategies.

Mammographic evaluation

Microcalcifications are the most common mammographic manifestation of DCIS and are associated with malignancy in up to 35% of cases (93). Ninety percent of all carcinomas presenting as mammographic microcalcifications are in-situ lesions and 80% of these are usually DCIS (33, 93–95). Most of the calcifications represent calcium deposits on debris or secretions into the duct lumen, although calcifications can also be found in the duct epithelium (96). Microcalcifications in DCIS may be focal or diffuse, and they have a variable size and shape; their pleomorphism is best recognized by magnification mammography. Holland *et al.* described two different types of microcalcifications in DCIS: (a) those that are of the linear branching type and are associated with high nuclear-grade, comedo-type DCIS and (b) fine, granular calcifications, which are associated with micropapillary or cribriform lesions (lower nuclear grade and no necrosis) (97). However, comedo and noncomedo ductal carcinoma cannot be specifically identified by mammographic features (98). It should be emphasized that microcalcifications on mammography often underestimate the size of the tumour, particularly in cases of low-grade (well-differentiated) DCIS, in which substantial areas of tumour may not contain microcalcifications (18, 97, 99). Indeed, Holland *et al.* found that in 44% of micropapillary tumours, the lesions were more than 2 cm larger by histologic examination than by mammographic estimate, compared with only 12% of the pure comedo subtype (99). However, with state-of-the-art mammography (including magnification views) the extent of the disease was underestimated in only 14% of micropapillary tumours (97).

Atypical mammographic features of DCIS may include circumscribed nodules, ill-defined masses (~ 10% of DCIS), ductal asymmetry, architectural distortion, etc. (59, 100, 101). An interval change of the mammogram may be another reason to perform a biopsy; this finding is associated with malignancy in approximately 20% of cases with most of these malignancies being in-situ carcinomas (102, 103).

The role of other imaging modalities, especially breast magnetic resonance imaging (MRI), in staging the extent of DCIS within the breast has yet to be established.

Diagnostic biopsy

Recent mammographic evaluation (usually within 3 months) before biopsy (or definitive surgery) is needed to define the disease's extent and establish the appropriateness of breast-conservation therapy. The contralateral breast should also be evaluated; therefore bilateral mammography is required. In addition to routine mediolateral oblique and craniocaudal views, magnification views and any other special views that may be required should be obtained in an attempt to identify areas of calcified tumour that otherwise might no be apparent.

Since today most cases of DCIS are non-palpable lesions, detected on routine mammography, image-directed procedures are necessary to confirm the diagnosis and determine the treatment. Mammography is the imaging modality that is usually used for presurgical localization of the suspicious lesion (104, 105). Although ultrasound-guided biopsy may be useful for nonpalpable masses, it usually cannot be relied upon for biopsy of microcalcifications (i.e., the majority of DCIS) (104). Mammographically guided local excision is safe, accurate and cost effective method and achieves accurate removal of the abnormal area while avoiding excess sacrifice of normal breast tissue. The localization method can be

needle-hook wire, dye injection, or a combination of both (104). Localization should be precise and may require positioning of more than one wire.

From a technical point of view, it should be emphasized that the local excision of DCIS is not always a straightforward procedure. The incision should be long enough to permit removal of the specimen in one piece. Removal of the lesion in numerous fragments should be avoided because it precludes margin assessment and size determination (104). The goal at the time of excisional biopsy should be to perform a margin-negative resection that can serve as a definitive segmental mastectomy (local excision or lumpectomy), thereby avoiding the need for a second operation. However, in contrast to infiltrating breast cancer, which is generally a palpable mass, easily measured, and commonly excised with clear margins, DCIS is generally nonpalpable and nonvisible (mammographic finding) and may be difficult to excise with clear margins. Moreover, the entirety of the DCIS may not always be marked with microcalcifications, resulting in an underestimation and uncertainty of its real size on mammography (see above, mammographic evaluation). For the same reasons, the margins should be at least 1 cm, with 2 cm being preferable (104). These recommendations are based on the previously reported data by Holland *et al.*, who demonstrated that often the tumour extended more than 2 cm further on histologic examination than was estimated by mammography (see: Mammographic evaluation). Meticulous hemostasis is especially important. Hematoma formation may result in delaying radiation therapy, if planned. Furthermore, hematoma and subsequent scar formation produces changes that are difficult to interpret by both physical examination and mammography (104).

Following local excision, the surgeon should orient the specimen (e.g., superior, medial, lateral) for the pathologist, usually with sutures. Specimen radiography is then performed to confirm complete removal of the suspicious lesion. Magnification and compression of the specimen increase the resolution of the radiograph. Absence of the mammographic abnormality on the specimen radiograph usually indicates that it has not been removed. Extension of calcifications (or – less frequently – of the mass) to the margin of the specimen suggests that a residual tumor might be present in the breast and that further resection along that margin is indicated. After whole-specimen radiography, the specimen should be inked and then serially sectioned for pathologic examination to evaluate margin status and extent of disease (104). If a re-excision is required due to incomplete removal of the lesion, the involved margin at the previous biopsy site must be re-excised carefully to ensure negative margins of resection, avoid excess removal of breast tissue, and achieve good cosmesis. Proper orientation of the original biopsy specimen avoids removal of an already negative margin. When the site of inadequate margins is not known, a rim of tissue must be removed around the previous biopsy site. If the presence of residual microcalcifications on postoperative mammogram is the indication for re-excision, needle localization should be considered (104).

Fine needle aspiration cytology (FNAC) is unreliable because the diagnosis of DCIS implies accurate exclusion of stromal invasion, which can be accomplished only by microscopic examination of a histologically intact specimen to analyze the overall histologic architecture of the diseased tissue. Therefore, although cytologic aspirates of DCIS, obtained by FNAC, are generally interpreted as malignant, they cannot be reliably distinguished from an invasive carcinoma (104).

Stereotactic core needle biopsy – performed by experienced radiologists or surgeons – has recently gained popularity as a means of managing certain mammographic abnormalities (104, 106). However, not all DCIS lesions are amenable to stereotactic core-needle biopsy, for example, calcifications that appear faintly or are deep in the breast and close to the chest wall may be difficult to target with stereotactic core biopsy. For lesions suitable for stereotactic breast biopsy, multiple cores should be obtained, and the specimen radiographed to confirm an adequate sampling of microcalcifications. This diagnostic method should be used judiciously (107) and care should be taken not to completely excise all microcalcifications without placing a metallic marker to guide future surgical excision, if needed. Leaving some microcalcifications at the site is desirable, because if DCIS is diagnosed, they can accurately direct the surgeon for definitive excision (see above, preoperative mammographically guided localization). It should be emphasized that if a presurgical diagnosis of DCIS is made by percutaneous core-needle biopsy, areas of invasive carcinoma will be found in a significant percentage of cases (up to 20%) at the time of surgical excision, depending mainly on the tumour size and histologic subtype of DCIS (31).

FACTORS PREDICTING RECURRENCE

There is growing evidence that DCIS is not a single disease. Rather, this term encompasses a diverse group of lesions that differ with regard to their clinical presentation, mammographic features, extent and distribution within the breast, histologic characters, biologic markers, and biological behavior. Clinical

studies have indicated that these lesions vary in their propensity to recur or progress to invasive breast cancer. These findings suggest that some lesions may require no treatment other than wide local excision alone, whereas others may require complete excision and radiotherapy or even mastectomy. A means to determine reliably which patients with DCIS can be safely treated with excision alone, which patients require radiation therapy after local excision, and which patients require mastectomy is of crucial importance. Attempts to resolve this issue have focused on the identification of risk factors for local recurrence after breast-conservation therapy for DCIS.

Tumour size has been recognized as a prognostic factor. DCIS presenting as a mass (> 1 cm) is associated with a significantly higher incidence of occult invasion, multicentricity, axillary lymph node metastases, higher local recurrence rates, and worse overall and disease-free survival than those cases presenting as small, nonpalpable lesions incidentally diagnosed on screening mammography(19, 33, 59, 74, 108–111). Unfortunately, accurate determination of the size or extent of the lesion is not always easy, especially for the majority of DCIS presenting as non-palpable mammographic abnormalities (microcalcifications). In those cases, two modalities are available to estimate the size of the lesion: mammography and pathologic examination. The problems and/or limitations of mammography in estimating the size of DCIS have been discussed previously (see mammographic evaluation). Determination of the lesion size may also be difficult for the pathologist. Macroscopic examination of a specimen containing DCIS rarely reveals a grossly evident tumour that can be measured. Therefore, the assessment of size of the lesion often must be performed on the histologic sections. When the lesion is present in a single slide, the greatest dimension can be measured and reported. However, in many cases of DCIS, the lesion is present on more than one slide. In such cases, accurate determination of the size or extent of the lesion is not possible, unless the specimen has been examined in a sequential manner as described by Silverstein *et al.* (112), which, however, is not applicable on a routine basis in many pathology laboratories.

Complete tumour excision, confirmed by specimen radiography, evaluation of resection margins, and post-excision mammogram, is an important determinant of local control; in contrast, involved margins of resection have been identified as the most important independent prognostic variable for predicting local relapse (113–115). In the study by Solin *et al.*, the crude breast tumour recurrence rate was 29% for patients with close or positive margins compared with 7% for those with negative margins (116). Therefore, the assessment of surgical margins is probably the most important aspect of the pathologic evaluation of breast tumour excisions in patients being considered for breast-conservation therapy. Although the definition of 'positive' and 'negative' varies among institutions, microscopic extension of DCIS to surgical margins usually results in further surgery. The pathologist should clearly specify in the pathology report whether DCIS is transected at the surgical margins, and if not, how close the lesion is to the nearest margin. Unfortunately, margin evaluation may be a complicated process in some cases (117). For example, if a specimen is removed in more than one fragment, the margins cannot be evaluated. Similarly, it is often difficult – if not impossible – to provide an accurate assessment of the margin width in patients who undergo a reexcision of the biopsy site. This is particularly true if the margins of the initial excision are positive and a reexcision specimen shows no residual tumour. Furthermore, there is no standardized method for sampling margins, and margin evaluation is highly subject to sampling error. Thus, in many cases, the width of the final margins cannot be determined accurately.

The presence of residual malignant appearing calcifications on a post-biopsy mammogram signifies incomplete tumour excision and therefore is associated with an increased risk of recurrence; failure to remove these calcifications before radiation has resulted in a 100% recurrence rate(113, 115, 118, 119). It may be possible that the hypoxic malignant cells in the comedo-type DCIS (which is more frequently associated with microcalcifications) are less sensitive to radiation therapy; this emphasizes again the need for complete tumor excision before breast irradiation.

The presence of comedo necrosis has been associated with a higher recurrence rates after initial treatment of DCIS (54, 77, 120–122). In Lagios *et al's.* (63) series of 79 patients treated with lumpectomy, recurrence rates varied according to histologic subtypes. Patients with the micropapillary subtype had no recurrences (0 of 33), whereas those with evidence of comedo necrosis had a 16% recurrence rate (five of 31) and cases with the cribriform pattern with necrosis had a 40% recurrence rate (two of five). Length of follow-up is an important consideration in interpreting these data. For example, Solin *et al.* (123), in a study of DCIS with longer follow-up (10.3 years), showed that the risks for recurrence at 5 years with comedo necrosis and noncomedo necrosis histology were 11% and 2%, respectively. At 10 years, the risks were 17% for comedo necrosis histology and 15% for noncomedo necrosis histology ($P > 0.2$). In addition to higher recurrence rates, comedo subtype DCIS was also associated with shorter disease-free interval to recurrence. In the same study, the median interval

to local recurrence was 3.1 years for high-grade comedo lesions, compared with 6.5 years for other lesions (123).

Nuclear grade has been shown to be closely associated with increased recurrence rates, aneuploid or tetraploid DNA content, a greater likelihood of large S-phase fraction, overexpression of *c-erb*B-2, and to a lesser extent of p53, and a higher frequency of receptor negative status (69–72, 124–125). In an analysis of the influence of histologic grade on local recurrence, Solin *et al.* (64) noted recurrence rates of 20% for high-grade DCIS compared with 5% for low-grade lesions at 87 months of follow-up. Similar results were reported in the study by Lagios *et al.* (63) in which recurrence rates were projected as 28% for similarly defined high-grade DCIS and 6% for lower-grade DCIS at 120 months of follow-up. At 124 months of actual follow-up, local recurrence rates are 33% and 2.3%, respectively, for these two groups. The results of these and subsequent studies showed that the vast majority of local recurrences occur among 'poorly differentiated' subtypes, classified as high-grade (i.e., high-grade nuclear morphology, usually associated with comedo necrosis) (126). Recurrences following breast-conservation therapy of DCIS of low nuclear grade, with focal only or absent necrosis, are fewer and at greater interval than among cases with high-grade lesions.

The significance of a positive family history of breast cancer and young age remains controversial. Some studies reported a higher incidence of recurrences among young women (116, 118, 127, 128). Since local recurrence rates increase consistently with longer follow-up intervals, with a significant proportion of these recurrences appearing even more than 15 years after the initial diagnosis of DCIS, some investigators suggested that young patients with DCIS should be treated by total mastectomy, given their longer life span over which recurrences may develop, as well as the more aggressive behavior of breast carcinoma in young patients(129). Similarly, family history of breast cancer has been reported to be associated with increased recurrence rates(127). However, other studies have found no correlation between young age (113, 123, 130, 131) or family history (115, 118) and recurrence rates. Further studies are required to evaluate the prognostic significance of young age and of a positive family history in patients with DCIS.

Following the identification of factors indicative of aggressive-biology, classification systems of non-invasive breast cancer have undergone a fundamental change, from a strictly descriptive histologic nomenclature to a system than incorporates these prognostic factors and stratifies lesions based on their likelihood of recurrence. Silverstein *et al.* in 1995 (132) developed the Van Nuys classification system (Fig. 2), which is a highly reproducible and easy to apply. In this system, patients with DCIS were assigned to one of three groups based on the presence or absence of high nuclear grade and comedo necrosis group 1 had non-high grade DCIS without comedo necrosis, group 2 had non-high grade DCIS with comedo necrosis, and group 3 had high-grade DCIS with or without comedo necrosis. Two hundred and thirty-eight patients treated with breast preservation surgery (99 by excision alone and 139 by excision plus radiotherapy) for DCIS were retrospectively stratified into these three groups. There was a statistically significant difference in recurrence rates between the three groups (3.8% in group 1, 11.1% in group 2, and 26.5% in group 3). The 8-year

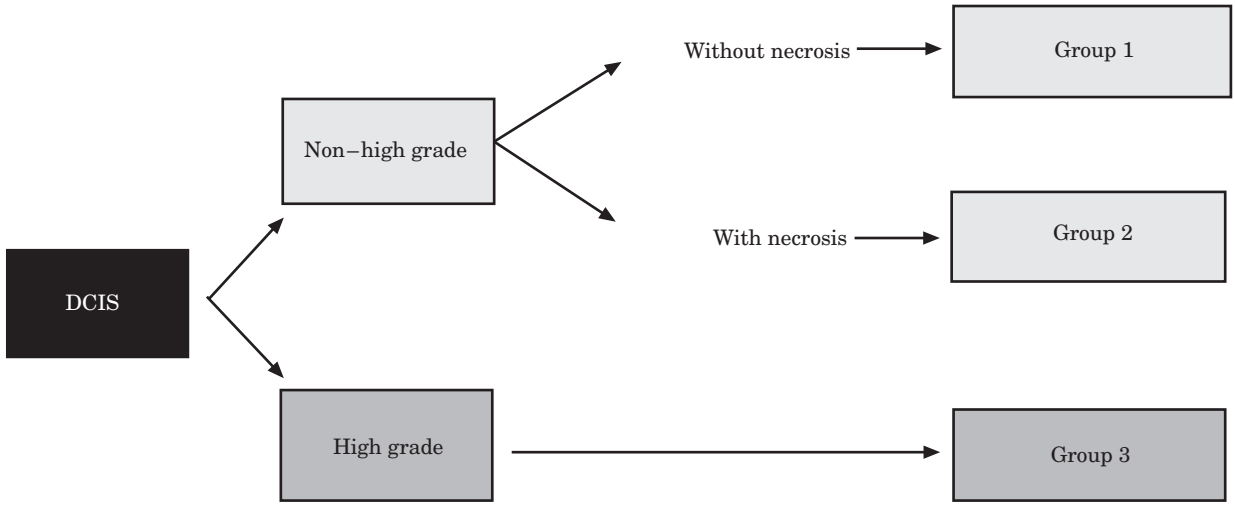

Figure 2 The Van Nuys classification system.

Table 2 The Van Nuys Prognostic Index

(VNPI) VNPI = A + B + C
A = Size Score
1 : Tumour size ≤ 15 mm
2 : Tumour size 16–40 mm
3 : Tumour size ≥ 41 mm
B = Margin Score
1 : Margins ≥ 10 mm
2 : Margins 1–9 mm
3: Margins < 1 mm
C = Pathologic classification score (see Van Nuys DCIS classification)
1 : Non-high grade lesions in the absence of comedo necrosis
2 : Non-high grade lesions in the presence of comedo necrosis
3 : High grade lesions with or without comedo necrosis

actuarial disease-free survivals were 93%, 84%, and 61%, respectively for the three groups ($p < 0.05$). Silverstein *et al.* suggested that non-high grade DCIS (group 1 and 2) can effectively be treated with breast-conserving surgery with or without radiotherapy. In group 3, even with radiation therapy, the local recurrence rate was estimated to be 30% at 7 years, and thus, for many patients in this group, mastectomy may be the procedure of choice.

The Van Nuys Prognostic Index (VNPl) (Table 2) has subsequently been proposed by Silverstein *et al.* (112, 133) as a tool to aid the complex treatment decision-making process. The VNPl stratifies DCIS patients according to three significant predictors or local recurrence: tumour size, width of surgical excision margins, and pathologic classification (based on the Van Nuys classification system, see above). Numerical values ranging from 1 (best) to 3 (worst) are assigned for each of the three predictors, as indicated in Table 2. The sum of these three scores results in the VNPI score, which ranges from the lowest (best) possible score of 3 to the highest (worst) possible score of 9. Based on the resultant VNPI score, either local excision, local excision plus radiotherapy, or mastectomy has been recommended. Silverstein *et al.* (112,133) studied 333 DCIS patients who were treated with breast-conservation therapy; these patients were retrospectively assigned a VNPI score and studied with local recurrence as the end point. The treatment has been lumpectomy alone in 195 patients and lumpectomy plus radiation therapy in 138. Patients with VNPI scores of 3 or 4 did not show a significant 8-year disease-free survival benefit from breast irradiation (100% vs. 97%, $P = 0.43$). Patients with intermediate VNPI scores of 5, 6, or 7 benefited by irradiation (8-year disease-free survival: 85% vs. 68%, $P = 0.017$). Although patients with a VNPI of 8 or 9 showed the greatest benefit with the addition of radiation therapy (8-year disease-free survival: 36% vs. 0%, $P = 0.03$), local recurrence rates exceeded 60% in 8 years, regardless of irradiation. Therefore, the authors concluded that patients with high scores (8 or 9) should be considered for mastectomy. In contrast, patients with VNPI scores of 3 or 4 should be treated with excision alone, since they do not benefit from radiation therapy. Treatment recommendations for the intermediate group (VNPI scores of 5, 6, or 7) are the most difficult. Overall, this group will benefit from radiation therapy after local excision. However, in this group the selection of the surgical procedure requires independent judgments that must be made by the physician and the patient. The VNPI may become a useful adjunct in therapeutic decision making; however, it was developed in a retrospective study and therefore – as suggested by Silverstein *et al.* (112) – the validity of VNPI must be independently and prospectively confirmed by other groups.

TREATMENT

The treatment of DCIS is currently less well defined than its invasive counterpart and continues to be the subject of considerable controversy. Since DCIS is an increasingly common incidental mammographic finding, it is expected that, as the use of mammography increases, so will the problem. Local treatment approaches that have been used for the treatment of DCIS include the following: (a) simple (total) mastectomy; (b) breast-conservation therapy (i.e., local excision plus definitive breast irradiation), or (c) local excision alone. Currently, the treatment controversies center around two points: which patients require mastectomy and whether or not all patients who elect breast-sparing treatment require radiation therapy.

Mastectomy

Traditionally, the treatment of DCIS has been mastectomy [with or without level I (low) axillary lymph node dissection and immediate or delayed breast reconstruction]. The rational for total mastectomy is based on the incidence of multifocality and multicentricity, as well as the possibility of occult invasion associated with DCIS. Mastectomy remains the standard of care with which other proposed therapeutic modalities should be compared; it achieves very low recurrence rates (~ 1%, range: 0–4%) and subsequent mortality from metastatic breast cancer (mean 1.3%, range: 0–4%)) (Table 3) (18, 19, 54, 75, 77, 79, 109–111, 114, 134–140). Failure of mastectomy to prevent recurrences may occur, especially in patients with very extensive DCIS; this may be due to the irreducible 3–5% of breast tissue that remains after a

Table 3 Risk of recurrence after mastectomy for DCIS

Author (Ref)	Year	Patients	Patients with recurrence	Follow-up (years)
Farrow (18)	1970	181	1	5–20
Kinne *et al.* (134)	1989	101	1	11
Ashikari *et al.* (139)	1977	92	0	11
Silverstein *et al.* (136)	1995	167	2	6.5
Arnesson *et al.* (114)	1989	28	0	6.4
Schuh *et al.* (137)	1986	52	1	5.5
Fisher *et al.* (54)	1986	28	1	3.2
Sunshine *et al.* (138)	1985	68	3	10
vonRueden-Wilson *et al.* (139)	1984	45	0	–
Westrbrook & Gallagher (109)	1975	60	1	5–25
Brown *et al.* (111)	1976	39	0	1–15
Carter and Smith (110)	1977	38	0	6.2
Rosner *et al.* (19)	1980	182	0	5
Lagios *et al.* (75)	1982	53	2	3.7
Fentiman *et al.* (79)	1986	76	1	4.8
Ciatto *et al.* (140)	1990	210	3	5.5
Fisher *et al.* (77)	1991	28	0	7.1
Total		1448	16 (1.1%)	

total mastectomy. This tissue can contribute to delayed de-novo invasive events arising in residual breast parenchyma containing DCIS, such as in the skin flaps, the axilla, and the chest wall. Since in older studies many patients had large palpable lesions, the few distant recurrences were most likely due to occult invasion (141). Therefore, breast cancer-related mortality – albeit minimal – is not completely avoided, even through the use of mastectomy (123).

Breast-conservation therapy (local excision plus radiotherapy)

Although mastectomy for DCIS is a highly effective method, it undoubtedly represents over-treatment in a substantial number of patients, particularly those with small, mammographically detected lesions. The acceptance of breast-conservation therapy for invasive carcinoma has stimulated great interest in the use of this technique for the management of DCIS. The results of many studies are now available which clearly show that, in carefully selected patients, breast-conservation therapy can achieve low recurrence rates (mean, 10%, range, 3–25%) and acceptable overall- and/or disease-free-survival (Table 4) (32, 64, 65, 82, 118–123, 127, 128, 136, 141–152). In these studies, about 50% of the tumours recurred as invasive cancer. Many of these recurrences can be salvaged with mastectomy (see below, treatment of recurrences). Deaths caused by breast cancer have been reported in up to 4% of these patients, with a median follow-up of about 10 years. Nowadays, as a result of accurate information about the curative potential of breast-conservation therapy, patients less frequently have mastectomy as a front-line treatment; the use of breast-conservation therapy in the treatment of DCIS increased from 26% in 1983 to 54% in 1992 (22, 153). Interestingly, recent and ongoing clinical trials in DCIS have not included mastectomy as standard treatment (120).

Negative margins of resection are important to minimize the ipsilateral breast tumour recurrence rate. For mammographically detected DCIS presenting as microcalcifications, all malignant calcifications must be removed before irradiation is initiated (see above, factors predicting recurrence). This is important, because there is evidence that DCIS – especially the well differentiated type – may be less radiosensitive than the more aggressive, less differentiated infiltrating cancers (154).

Breast irradiation usually begin as soon as the patient has healed adequately form the surgical procedure, usually within 2 to 4 weeks after uncomplicated breast-conserving surgery. Whole-breast irradiation therapy is delivered using opposed tangential fields to a dose of 4500 to 5000 cGy at 180 to 200 cGy per fraction. Each field should be treated on a daily basis, 5 days a week (59). The need for delivering an additional boost dose to the primary site remains controversial. When used, boost irradiation usually is delivered using electron beam or interstitial implantation to a total dose of approximately 6000 to 6600 cGy to the primary tumour site. Nodal irradiation is unnecessary.

Table 4 Rate of recurrence after breast-conservation therapy for DCIS

Author (Ref)	Year	Patients (N)	Follow-up (yr)	Patients with recurrence N (%)	Patients with invasive recurrence N (%)
Kurtz *et al.* (121)	1989	44	5	3 (7 %)	3 (100 %)
Solin *et al.* (142)	1990	51	5.7	5 (10 %)	2 (40 %)
Bornstein *et al.* (128)	1991	38	6.8	8 (21 %)	5 (63 %)
Silverstein *et al.* (143)	1992	103	3.7	10 (10 %)	5 (50 %)
Fisher *et al.* (144)	1989	27	7	2 (7 %)	1 (50 %)
Kuske *et al.* (122)	1993	70	48	3 (4 %)	3 (100 %)
Fisher *et al.* (120)	1993	399	43	28 (7 %)	8 (29 %)
Solin *et al.* (123)	1996	268	10	45 (17 %)	24 (53 %)
Hafty *et al.* (145)	1990	60	3.6	4 (9 %)	1 (25 %)
Solin *et al.* (146)	1991	259	6.6	28 (11%)	14 (50 %)
Silverstein *et al.* (136)	1995	133	7.8	16 (12 %)	8 (50 %)
Cataliotti *et al.* (82)	1992	34	7.8	3 (9 %)	3 (100 %)
Ray *et al.* (147)	1994	56	5	5 (9 %)	1 (20 %)
Baird *et al.* (65)	1990	8	3.3	2 (25 %)	1 (50 %)
McCormick *et al.* (148)	1990	54	3	10 (18 %)	3 (30 %)
Stotter *et al.* (149)	1990	42	7.7	4 (9.5 %)	4 (100%)
Zafrani *et al.* (150)	1986	55	4.6	3 (5.5 %)	1 (33 %)
Ringberg *et al.* (32)	1991	21	7	3 (14 %)	3 (100 %)
Solin *et al.* (64)	1993	172	7	16 (9 %)	7 (44 %)
VanZee *et al.* (127)	1996	63	6.2	10 (16 %)	3 (30 %)
Fowble *et al.* (118)	1997	110	5.4	3 (3 %)	3 (100%)
Sneige *et al.* (119)	1995	49	7.2	5 (10 %)	3 (60 %)
Cutuli *et al.* (151)	1992	34	4.7	3 (9 %)	1 (33 %)
Rechi *et al.* (152)	1985	40	3.7	4 (10 %)	2 (50 %)
Total		2190		223 (10 %)	109 (49 %)

Certain factors, such as history of collagen vascular disease (especially scleroderma and lupus erythematosus), previous therapeutic irradiation to the breast or chest, and pregnancy (104), preclude the use of irradiation (and therefore of breast-conservation therapy) in the treatment of patients with DCIS, because of toxicity concerns.

Local excision alone

Lagios *et al.* first suggested local excision only without postoperative irradiation as treatment for selected patients with DCIS (75,155). These investigators found that in 115 mastectomy specimens, occult invasive breast cancer was identified only in breasts in which DCIS exceeded 45 mm and occurred in nearly 50% of breasts with DCIS larger than 55 mm in diameter. Subsequently, 79 patients with mammographically detected DCIS were treated by margin-negative wide local excision alone. The overall recurrence rate at 44 months was 10%, with 92% of the recurrences found in the same quadrant as the primary lesion and in the vicinity of the biopsy site. Fifty percent of the recurrences were invasive, but all were identified early by routine screening. After a longer follow-up (124 months) of the same cohort of patients, local recurrence was 16% overall – 33% for the subgroup of patients with high-grade lesions vs. 10% for intermediate-grade lesions and only 2% for patients with low- or intermediate-grade lesions.

Other recent studies have attempted to identify and treat highly selected patients with excision alone (i.e., without definitive breast irradiation) (Table 5) (40, 44, 62, 63, 65, 82, 114, 120, 143, 144, 156–164). The patients in these studies were highly selected for favourable tumour characteristics, such as small tumour size, detection by mammographic abnormalities only, pathologically confirmed negative margins of resection, and favourable pathologic characteristics (e.g., low-grade and/or noncomedo subtype). Local excision alone was associated with a high recurrence rate (mean: 19%, range: 6 to 63%) (Table 5). This wide range of recurrence rates reflects different inclusion criteria, different rigor of pathologic assessment, and different follow-up times. About half of the tumours recurrent as invasive cancer (mean, 19%, range: 20% to 100%) (Table 5). The histologic subtype of DCIS was found to be an important predictor of the risk of local recurrence after treatment with excision alone. Patients with high-grade comedo subtype DCIS had higher local recurrence

Table 5 Rate of recurrence after wide local excision alone for DCIS

Author (Ref)	Year	Paitents (N)	Follow-up (yr)	Patients with recurrence, N (%)	Patients with invasive recurrence, N (%)
Carpenter *et al.* (156)	1989	28	3.1	5 (18 %)	1 (20%)
Arnesson *et al.* (114)	1989	38	5	5 (13 %)	2 (40 %)
Lagios *et al.* (63)	1989	79	3.7	8 (10 %)	4 (50 %)
Graham *et al.* (157)	1991	37	8	14 (38 %)	7 (50 %)
Gallagher *et al.* (158)	1989	13	8.3	5 (38 %)	3 (60 %)
Price *et al.* (159)	1990	35	9	22 (63 %)	12 (55 %)
Fisher *et al.* (144)	1989	21	6.9	9 (43 %)	5 (56 %)
Fisher *et al.* (120)	1993	391	3.6	64 (16 %)	32 (50 %)
Schwartz *et al.* (62)	1992	72	4	11 (15 %)	3 (27 %)
Silverstein *et al.* (143)	1992	26	1.5	2 (8%)	1 (50 %)
Ottesen *et al.* (160)	1992	112	4.4	25 (22 %)	5 (20 %)
Cataliotti *et al.* (82)	1992	46	7.8	5 (11 %)	5 (100 %)
Page *et al.* (40)	1982	25	16	7 (28 %)	7 (100 %)
Temple *et al.* (161)	1989	17	6	2 (12 %)	2 (100 %)
Baird *et al.* (65)	1990	30	3.2	4 (13 %)	1 (25%)
Eusebi *et al.* (44)	1994	80	17.5	16 (20 %)	11 (69 %)
Salvadori *et al.* (162)	1997	74	2.6	10 (14 %)	6 (60 %)
Schreer *et al.* (163)	1996	102	4.7	24 (24 %)	10 (42 %)
Sibbering and Blamey (164)	1997	48	4.8	3 (6 %)	1 (33 %)
Total		1274		241 (19%)	118 (49%)

rates than patients with low-grade noncomedo DCIS following treatment with local excision alone (62, 63, 155, 165). Limitations of these studies include the relatively small number of patients, the highly selective nature of patients studied, and the limited follow-up time. For an accurate interpretation of these data, a long follow-up is required, since local recurrence can occur even 15–25 years later (74, 112, 133, 158, 159, 166). However, these studies suggested that local excision alone may be appropriate therapy for a carefully selected subgroup of patients (see below, practical recommendations). This is an important finding, since breast irradiation has its own side effects and ideally should be offered to those patients with DCIS likely to obtain a benefit; moreover, it changes the texture of the breast, making subsequent mammographic evaluation more difficult to interpret, and, most important, its use precludes additional breast irradiation and breast-conservation therapy should a invasive breast cancer develop either as a metachronous cancer or as recurrent tumour.

Mastectomy vs. breast-conservation therapy

The largest study comparing breast-conservation therapy to mastectomy is the non-randomized study of 227 cases of DCIS without microinvasion by Silverstein *et al*. (143). Patients with tumours smaller than 4 cm with microscopically clear margins were treated with wide local resection and radiation therapy. Patients with tumours larger than 4 cm or positive margins were treated with mastectomy. The disease-free survival at seven years was 98% in the mastectomy group vs. 84% in the breast-conservation therapy group (P=0.038) with no difference in overall survival. With close follow-up the results of salvage surgery were excellent, and an increase in local recurrences has not affected overall survival.

The same group (136) retrospectively evaluated 167 women with DCIS who had mastectomy and 133 who received breast-conservation therapy. There was a significant difference of those treated with mastectomy (98% vs. 81%, P=0.0004). Multivariate analysis confirmed nuclear grade as the only significant predictor of local recurrence (P=0.02) or invasive local recurrence (P=0.03) in patients with DCIS treated with excision and radiation therapy. There was no difference in breast cancer-specific survival or overall survival between the two treatment groups.

The NSABP B-06 was a randomized trial designed to compare local excision alone, breast-conservation therapy, and mastectomy in patients with early invasive breast cancer (144). A subset of 76 patients was found to have DCIS on subsequent pathologic review (77). The lesions were larger than 10 mm in 84% of cases, and moderate or marked comedo necrosis was present in 60% of specimens. Twenty-seven patients received breast-conservation therapy, 21 had excision alone, and 28 were treated with mastectomy. Two patients (7%) who received breast-conservation therapy and nine (43%) who had local

excision alone had recurrence in the ipsilateral breast. No tumour recurrence occurred in the mastectomy group. Of the 11 recurrences, six (55%) were cases of invasive breast cancer. The average time to in-breast recurrence was 35 months. The recurrent tumours were morphologically similar to the original ones. On multivariate analysis, the only feature associated with a decreased risk for recurrence was the use of radiotherapy.

Local excision alone vs. breast-conservation therapy

The NSABP-B17 was a long-term randomized trial specifically designed to compare local excision (lumpectomy) alone with breast-conservation therapy for DCIS (120). In this trial, 818 women with mammographically or clinically detected tumours were studied. Seventy-three percent of the lesions were smaller than 1 cm, and 43% could not be measured grossly (<0.1 cm). After a mean follow-up of 43 months, the 5-year event-free survival rate was significantly better in the breast-conservation therapy arm than in the local excision arm (84.4% vs. 73.8%, P=0.001). The event-free survival rate was estimated by using the presence of ipsilateral or contralateral breast cancer, regional or distant metastases, a second primary tumour other than a breast tumor occurring after surgery, or death without recurrent disease as an event. The 5-year event-free survival rate was 85% for the excision plus radiation therapy group and 74% for the lumpectomy-alone (wide local excision) cohort (P=0.0001). The improvement in event-free survival was due to a decrease in local recurrence in the breast-conservation therapy group: 7% vs. 16.5% in the lumpectomy-alone group. At 5 years, invasive recurrences decreased from 50% of the total recurrences after wide local excision alone to about 27% of those treated with radiotherapy. This trial has been criticized for several possible flaws such as the relatively short duration of follow-up (mean 43 months), lack of subset analysis to assess the impact of histologic type, size of lesion (only 8% of the tumours were >2 cm), or mode of presentation (i.e., palpable mass vs. mammographic abnormality) (167). Recently published pathologic findings from the NSABP B17 study implicate comedo necrosis and margin status as independent predictors of local necrosis (168). In 1997, the results of the NSABP B-17 trial were updated (169). For this analysis, 814 patients were eligible for evaluation, with a mean time in the study of 90 months. All patients had been followed for more than 5 years, and 35% had been followed for more than 8 years. The total number of ipsilateral tumour recurrences was 151, and 70 (46.4%) recurrences were invasive. Most of the ipsilateral breast tumour recurrences were at or near the original lesion. This update confirmed the original conclusions of NSABP B-17 trial that ipsilateral breast tumour recurrence of both invasive and nonivasive breast cancer is significantly reduced by post-lumpectomy radiation therapy. In accordance with these data are the findings from the NSABP B-06 trial (see above, mastectomy vs. breast-conservation therapy).

Concerns about breast-sparing treatment

The fact that most women with invasive cancer do not require mastectomy highlights a paradox of using a operation for a non-invasive cancer that is more extensive than that for the disease one is trying to prevent. There are, however, some concerns about the results and the role of breast-sparing treatment (breast-conservation therapy or local excision alone) in the management of DCIS, that should be highlighted. As previously reported, nearly half of the recurrences after primary treatment for DCIS occurred as invasive cancer (see Tables 4 and 5), imparting a potential for systemic metastasis and death from a lesion which should theoretically been cured by complete local removal. Despite the fact that local recurrences following breast-sparing therapy for DCIS do not carry the dismal prognosis of chest wall recurrences after mastectomy (170) and can usually be treated successfully with a high probability of cure (see below), it should be emphasized that this is clearly an unfavourable and potentially preventable treatment failure for a pre-cancerous lesion with a malignant potential. Unlike local breast recurrences after breast conservation for invasive breast carcinoma, an invasive recurrence after a non-invasive primary lesion does represent a significant progression of the disease and conceivably could worsen the ultimate prognosis (159, 171). Furthermore, these recurrences require additional therapy and may be psychologically devastating to the patient, especially when they are invasive cancers.

Finally, in comparing mastectomy vs. breast-sparing therapy, it should be taken into consideration that patients currently selected for breast-conservation therapy or local excision alone are the most favourable cases, whereas patients selected for treatment with mastectomy typically have unfavourable characteristics (e.g., larger tumour size, diffuse microcalcifications, or positive margins of excision). In a report from a single institution, Silverstein *et al.* (143) found that there were differences for the patients selected to undergo mastectomy vs. excision plus radiation vs. excision alone for mean tumour size (37 mm vs. 14 mm vs. 10 mm, respectively), nonpalpable

presentation (62% vs. 86% vs. 85%, respectively), and involved margins on initial biopsy (68% vs. 31% vs. 31%, respectively). These considerations again emphasize the effectiveness of total mastectomy in the treatment of DCIS and can explain why it is still considered the standard of care to which all other treatments should be compared.

Axillary lymph node dissection

In general, axillary lymph node dissection (ALND) is considered unnecessary in the treatment of DCIS. The yield of axillary lymph node metastases is 1–2% (172, 173), but it approaches 0% when the breast lesion is detected mammographically (129, 134, 139, 174). Therefore, ALND is not routinely indicated (172). On the other hand, lesions with microinvasion have a potential for metastasis. The challenge for both the surgeon and the pathologist lies in identifying those lesions with microinvasion. As previously reported, the risk for microinvasion correlates with the size of the primary lesion and the presence of some specific histologic features, such as high-nuclear grade or comedo-type DCIS. Therefore, ALND is usually indicated for large (>3 cm) tumours, which frequently have a high nuclear grade and are of the comedo subtype and in which microinvasive disease may be present in an unsampled area of the specimen. Frequently, in these cases, mastectomy is elected as the appropriate surgical approach and a level I (low) ALND can be performed simultaneously during the resection of the axillary tail of Spence. If a clinically suspicious node is found during surgery, a frozen section should be performed, followed by a level I and II (partial) ALND if the node is positive. This technique adds minimal additional time and morbidity to the procedure, and it may provide the only evidence of occult invasion, with significant implications for prognosis and adjuvant treatment (49). ALND is also indicated in cases with palpable axillary lymphadenopathy or in cases of invasive local recurrence (175). In summary, there is no definitive indication for ALND in the management of pure DCIS. ALND should be reserved for lesions showing microinvasion (154, 172).

Tamoxifen

Several investigators have studied expression of oestrogen and progesterone receptors in DCIS. Oestrogen receptor activity has been documented in 30–60% of DCIS and was found to be associated with the noncomedo subtype and lack of *c-erb*B-2 overexpression (176–179). These findings suggest that hormone receptor activity in invasive breast carcinoma probably derives from such activity in its precursors and that antiestrogen medications may be an effective treatment in selected patients (178, 179). Potential primary prevention medications, such as tamoxifen (180) and raloxifen (181), have been found to reduce breast cancer risk. For women who have already had one primary breast cancer, the risk of a second primary in the contralateral breast has been shown to be reduced by as much as 40% with the use of adjuvant tamoxifen (182). The NSABP P-1 project compared prophylactic tamoxifen with placebo in high-risk women and found that tamoxifen reduced the risk of invasive cancer by 49% during a median follow-up of 55 months (183). However, the role of tamoxifen in the treatment of DCIS remains undefined. Two studies are now in progress to evaluate the effectiveness of tamoxifen in reducing recurrence in patients with DCIS. The NSABP B-24 trial[1] and the United Kingdom Committee for Cancer Research DCIS trial are both evaluating the role of tamoxifen in preventing subsequent invasive and in situ breast cancer in both the ipsilateral and contralateral breasts. At present, tamoxifen should be used as adjuvant treatment for patients with DCIS only in the context of a clinical trial.

Practical recommendations

Although the available treatment options for DCIS are similar to those used for management of invasive breast cancer, evidence regarding the safety and efficacy of breast-sparing therapy for DCIS is less conclusive. Until more decisive data from ongoing clinical trials become available, it seems prudent to offer mastectomy with the option of immediate or delayed breast reconstruction to patients with characteristics known to be associated with a substantial risk of locoregional recurrence and decreased survival. Neither tumour size nor histologic type is an absolute indication for mastectomy. However, the risk of occult breast cancer increases with the size of DCIS; moreover, local excision of large tumours is associated with a poor cosmetic result. Therefore, large (>3) or extensive DCIS that can be removed with only a small negative margin should be considered as an indication for mastectomy. This is particularly true in a patient with a small breast in which an adequate resection would result in a significant

[1]This trial has since been published. See Firher B, Dignam J, Wolmark N *et al*. Tamoxifen in the treatment of intraductal breast cancer. National Surgical Adjuvant Breast and Bowel Project B-24 randomized controlled trial. *Lancet* 1999; **353**: 1993–2000.

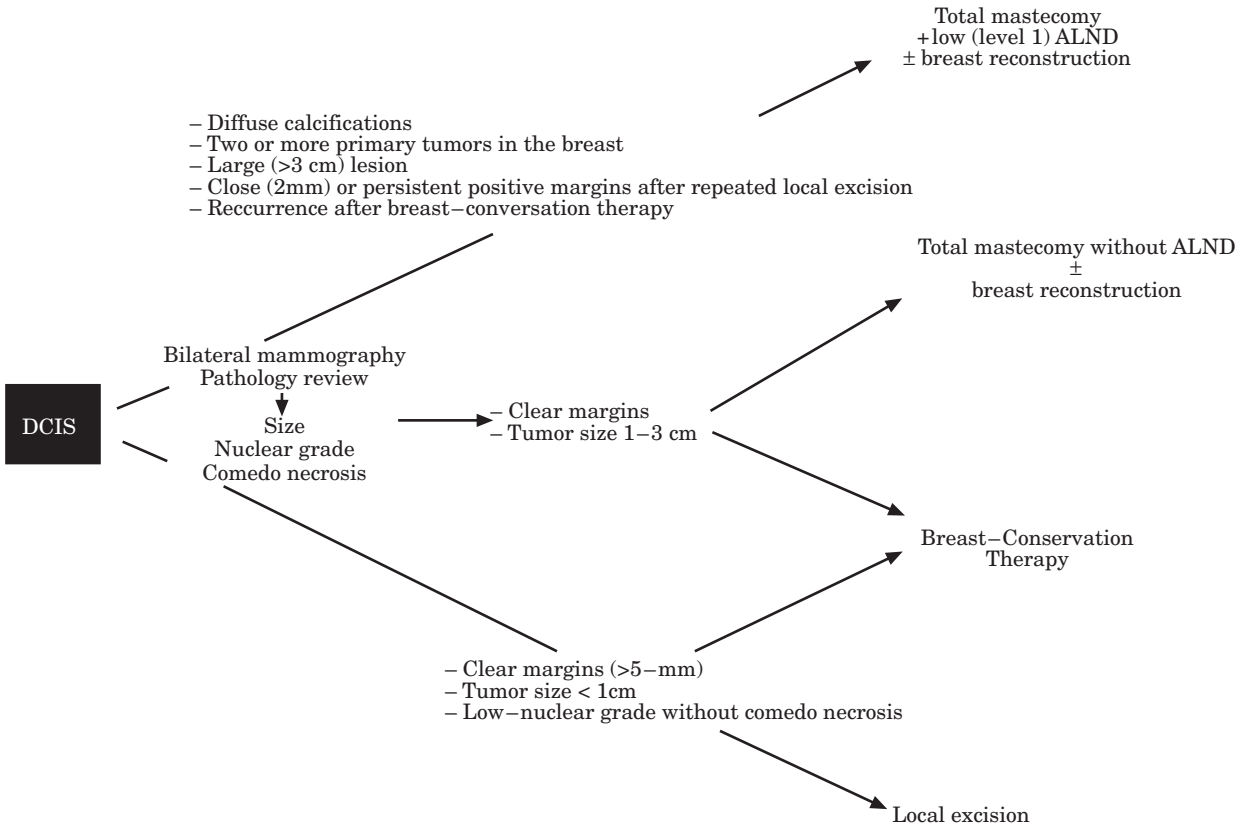

Figure 3 Proposed algorithm for the management of DCIS.

cosmetic alteration that is unacceptable to the patient, especially when considering the uncertainties in tumour size estimations (see above). For each patient, the risk:benefit ratio of breast conservation must be carefully assessed, and consideration must be given to mastectomy with breast reconstruction as a valuable treatment alternative (59). Therefore, indications for mastectomy are diffuse disease (evidenced as diffuse microcalcifications) or presence of two or more primary tumours in the breast, large lesions (> 3 cm)[2], with a high-grade comedo subtype histology, and persistent positive margins after repeat local excision. Mastectomy is also indicated for the treatment of local recurrence following breast-conservation therapy (Figure 3). Indications for breast-conservation therapy include localized DCIS, less than 3 cm, without evidence of gross multicentricity or diffuse malignant calcifications. However, the difficulties in measuring the size of DCIS (see above) makes definitive recommendations difficult. Local excision alone may be applied with caution in carefully selected patients. This approach may be most appropriate in cases of small DCIS (< 1 cm), especially of the noncomedo low-grade subtype and with clear specimen margins (> 5 mm). Figure 3 represents an algorithm proposed for the management of patients with DCIS.

Patient needs and expectations should be seriously taken into consideration in the surgical decision making; thus, mastectomy is probably the best choice for patients who want the highest disease-free and overall survival rate, and for those who are not willing to assume any increased risk, no matter how small it is. The surgeon should discuss the benefits and disadvantages of mastectomy (usually with breast reconstruction) compared with breast-sparing treatment on an individual basis. The controversies, risks, uncertainties, and limitations are discussed in detail with and comprehended by the patient. Furthermore, the patient should understand the need for a life-long surveillance following initial treatment for DCIS, especially following breast-sparing therapy.

[2]Some authors have proposed larger tumor size (> 4 cm) as an indication for mastectomy (3, 143). However, the larger the tumour, the more difficult to achieve complete tumour removal with satisfactory cosmetic result

DUCTAL CARCINOMA IN SITU ASSOCIATED WITH INVASIVE BREAST CANCER

The amount of the DCIS associated with infiltrating breast carcinoma varies widely, and the assessment of its extent is highly subjective. Infiltrating carcinomas with a prominent DCIS, both within the tumor and any DCIS around or beyond the limits of the invasive component, are interpreted as infiltrating carcinoma with extensive in-situ component (184). Schnitt *et al.* defined infiltrating ductal adenocarcinoma with an extensive intraductal component (EIC) as an invasive tumour in which 25% or more of the overall area involved by the invasive carcinoma is composed of DCIS, while DCIS also occurs both within the invasive carcinoma and beyond an imaginary line drown around the area of invasive carcinoma (185). The association of abundant DCIS within the tumour was associated with a tendency to also have DCIS beyond the tumour margin and multicentric carcinoma. Identification of an EIC appeared to be important prognostically in assisting clinicians to determine the optimal therapeutic approach. EIC was proposed as a contraindication to breast-conservation therapy, because of association with a higher rate of local recurrence (up to 25%) and treatment failure (185–188). However, further work showed that EIC significantly affects local control rates only when the non-invasive process (DCIS) contributes to the residual tumour load in the breast. With complete excisions for EIC-positive invasive breast carcinomas, irradiation provides a local control rate equal to that of EIC-negative lesions, and therefore EIC *per se* should not be an absolute contraindication to breast-conservation therapy unless substantial residual DCIS remains in the breast (141, 189).

After treatment, all patients with DCIS should have surveillance to facilitate early detection of subsequent malignancies. This follow-up should be as comprehensive as that of women with invasive breast carcinoma. Recent studies have indicated that in patients with DCIS treated by both local excision alone and breast-conservation therapy, the time course to local recurrence may be quite protracted. This is particularly true for the low-grade DCIS. For example, Page *et al.* have reported invasive carcinoma in the ipsilateral breast 20 to 30 years after a diagnostic biopsy which showed low grade DCIS (41). Similarly, among patients treated by breast-conservation therapy, Solin *et al.* noted that the local recurrence rate among patients with low grade DCIS increased with increasing length of follow-up (190). In this study, the actuarial risk of local recurrence for patients with low grade DCIS was 2% at 5 years, 5% at 8 years, and 15% at 10 years. This emphasizes the need for a comprehensive, life-long surveillance following initial management.

Following breast-sparing treatment, a post-surgical mammogram of the treated breast should be obtained to evaluate for residual microcalcifications. In addition, an ipsilateral mammogram should be obtained 3–4 months after the completion of radiation therapy to establish a new baseline. Follow-up of patients after breast-sparing treatment involves a twice-yearly physical examination and annual bilateral mammography for 5 years, with an annual physical examination and bilateral mammogram thereafter. It is important to know that postoperative and irradiation mammographic changes often are present as suspicious lesions. These changes include masses (postoperative fluid collections and scarring, which can result in the formation of a speculated mass mimicking tumour), oedema, and skin thickening. Postsurgical and radiation oedema, skin thickening, and postoperative fluid collections are most marked in the first 6 months. For most patients, radiographic changes slowly resolve after the first 6 to 12 months and show stability within 2 years. Each mammogram should be compared in sequence with the preceding study so that it can be accurately interpreted, using routine mediolateral oblique, craniocaudal, and magnification and spot compression views, if needed.

Furthermore, all patients (following either mastectomy or breast-sparing treatment) should be monitored closely for new primary cancer in the contralateral breast. The risk that a new primary cancer will appear in the contralateral breast after treatment for DCIS approaches two to five times the risk of a first primary breast cancer and is approximately the same as the risk for a contralateral new primary cancer after invasive cancer (33). Therefore, the contralateral breast should undergo clinical examination and mammographic evaluation annually. However, more frequent intervals may be needed depending on clinical or radiographic findings.

TREATMENT OF RECURRENCES

Several studies have reported the outcome of patients with tumour recurrence after primary tumour treatment (114, 121, 128, 156, 191). Solin *et al.* (191) reported 42 recurrences in patients with DCIS who received breast-conservation therapy: 23 had invasive carcinoma, and 19 had DCIS. Mastectomy was used for local salvage treatment in 40 patients, and local excision in two. Two patients received adjuvant chemotherapy, tamoxifen treatment was started in eight patients, and both adjuvant chemotherapy and tamoxifen were given to one patient. Thirty-two

patients did not receive systemic therapy. The overall survival rate at 5 years was 78%, and the 5-year cause-specific survival rate was 84% (191). Price *et al.* (159) followed 60 patients who had 26 recurrences after treatment. Eight patients had local excision alone, 10 received breast-conservation therapy, seven had mastectomy, and one received radiotherapy alone. Distant metastases developed in two patients with and two patients without local recurrence. Graham *et al.* (157) reported no cancer-related deaths among 14 patients who had recurrence after primary treatment for DCIS, seven of whom had invasive breast cancer. All patients (N=53) had had surgery as primary treatment (37 had lumpectomy alone). The salvage treatment was breast-conservation therapy in six patients, mastectomy in four patients, local excision alone in two patients, and radiotherapy alone in two patients. Solin *et al.* (123) in their collaborative multi-institutional trial studied the subset of patients with local recurrence after initial treatment using breast-conservation therapy; they showed 5-year actuarial rates of overall survival of 78% and cause-specific survival of 84% after salvage treatment. The 5-year actuarial rate of freedom from distant metastases was 86%. Of note, none of the patients whose local recurrence was intraductal carcinoma of whose local recurrence was detected with mammographic findings alone developed distant metastatic disease after salvage treatment. Therefore, local recurrences following the initial treatment of DCIS with breast-conservation therapy can be salvaged with high rates of survival and freedom from distant metastases and they have not the ominous prognosis that has been shown for chest wall recurrences after mastectomy (123, 170). Other studies, however, have suggested that locoregional recurrence in this setting could possibly result in a diminished chance of survival; these studies documented a 30% (42) and 43% (40) rate of carcinoma-related deaths among women with local recurrence after breast sparing treatment of DCIS. In contrast, distant metastases in the absence of local recurrence is rare, with an incidence of less than 1% (120, 123, 146). Simultaneous local-distant first failure is also rare, with an incidence of less than 1% (120, 123, 146). Distant metastases can also be associated with contralateral breast cancer (123). There is, therefore, evidence that a substantially greater rate of distant metastasis exists among women with local recurrence than among those without local recurrence after breast-conservation therapy for DCIS; consequently, the long-term risk after recurrence with invasive carcinoma needs to be better defined.

In summary, although no consensus exists, most authors recommend mastectomy for patients with recurrence if breast-conservation therapy was the initial management (175, 191). Nearly all patients who develop a non-invasive recurrence are salvaged with mastectomy, and approximately 75% of those with an invasive recurrence are salvaged (59). Selected patients initially treated by lumpectomy alone may also undergo breast-conservation therapy at the time of relapse according to the same strict guidelines of tumor margin clearance required for the primary lesion; radiation therapy should be given following local excision. The use of systemic therapy in patients with invasive recurrence should be based on standard criteria for invasive breast cancer.

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